VIA FACSIMILE AUGUST 4, 2003

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Ruben et al.

Docket No.: PZ003P4

Application No.: 09/852,659

Group Art Unit: 1636

Filed: May 11, 2001

Examiner: D. Sullivan

For: Secreted Protein HPMBQ91 (As Amended)

#25, Plunkett 8/6/03

RESPONSE UNDER 37 C.F.R. § 1.111

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

In response to the outstanding Office Action dated April 3, 2003 (Paper No. 23), please consider the following remarks. Applicants submit concurrently herewith: (a) a Fee Transmittal Sheet; (b) a Petition for Extension of Time of one month, to and including August 4, 2003, (August 3, 2003 being a Sunday; *see* 35 U.S.C. § 21); and (c) Exhibit A (alignment of NKB sequences). Applicants note that an Information Disclosure Statement is being submitted concurrently herewith under separate cover.

Claims 24-35 and 56-75 are pending.

I. Summaries of Interviews

Applicants thank Examiners Sullivan and Ketter for the interviews on February 27 and March 6, 2003, summaries of which were attached to Paper No. 23. To the extent that it may be required, Applicants provide summaries of these interviews below.

During the interview of February 27, 2003, the rejection of claims 27, 33 and 36-75 under 35 U.S.C. § 112, first paragraph for alleged lack of written description was discussed. Applicants argued that claims directed to proteins consisting of amino acid fragments of a disclosed polypeptide are adequately described by the disclosure of the full-length polypeptide. During this interview, Examiner Sullivan also indicated the possibility of a rejection being made under 35 U.S.C. § 101. After discussing the issue of the

description of fragments of SEQ ID NO: 85 with a Practice Specialist, Examiner Sullivan contacted Applicants in the interview of March 6, 2003 to indicate that, indeed, the disclosure of the full-length polypeptide provided adequate support for claims directed to fragments of this polypeptide. The rejection was withdrawn in Paper No. 23.

II. Rejection of the Claims Under 35 U.S.C. §§ 101 and 112, First Paragraph

Claims 24-35 and 56-75 were rejected under 35 U.S.C. § 101 for allegedly lacking patentable utility. *See* Paper No. 23, page 2, fifth paragraph. More specifically, as stated in Paper No. 23, page 3, first paragraph, "the utilities set forth do not rise to the requisite level of specific and substantial unless the function of the polypeptide molecule is known or the expression of the polypeptide can be correlated with a specific disease or condition."

In response, Applicants respectfully disagree and traverse.

Although the Examiner has acknowledged that Applicants have asserted "uses for the claimed polypeptides, and antibodies raised using the polypeptides, including ... diagnosis of diseases and conditions of the reproductive and embryonic systems" (Paper No. 23, pages 2-3), the Examiner does not address the specification's teaching that the claimed protein "modulates smooth muscle or vascularization associated with reproduction" (page 35, lines 14-15), and thus would be "useful for the diagnosis and treatment of reproductive and embryonic disorders" (page 36, lines 11-12), such as preeclampsia or eclampsia (page 229, line 10). Applicants respectfully assert that this asserted utility is specific, substantial, and credible, especially in light of the well-known properties of the tachykinin family.

In particular, it was well-known in the art prior to the filing date of the instant application that members of the tachykinin family were involved in preeclampsia and pregnancy-induced hypertension. For example, Hansen *et al.* (submitted as IDS reference J) show that Substance P (a member of the tachykinin family, now known as TAC1) increases uterine blood flow in rabbits and relaxes human intramyometrial arteries and fetal stem villous arteries, providing a role for tachykinins in the regulation of uteroplacental blood flow in pregnancy. Further, Knock and Poston (submitted as IDS reference H), showed that bradykinin, known to stimulate the release of tachykinins, induces relaxation in arteries of normotensive pregnant women, and to a lesser extent, in women with preeclampsia. Thus, it was well established that members of the tachykinin

family were involved in preeclampsia and pregnancy-induced hypertension. Accordingly, based on the teachings in the specification, it would have been readily apparent to one skilled in the art at the time of filing that the claimed polypeptide would more likely than not be useful in the diagnosis and treatment of preeclampsia and pregnancy-induced hypertension, as asserted in the specification.

This asserted utility is not only specific, substantial, and credible, but indeed true. As described in Brownbill *et al.* (submitted as IDS reference K), neurokinin B (NKB) induces dilation of the fetal vasculature, causing a reduction in fetal blood pressure. Brownbill *et al.* conclude that NKB likely has a significant role in preeclampsia, vasodilating the fetoplacental circulation in compensation for the reduced blood flow through the uterine circulation. Additionally, Page *et al.* WO01/36979, published May 25, 2001 (submitted as IDS reference B) and Page *et al.* (2000) Nature 405:797-800 (submitted as IDS reference D) teach that detection of the NKB precursor of the instant invention by the placenta provides a diagnostic tool for predicting the onset of preeclampsia and pregnancy-induced hypertension. Further, Swiss-Prot entry Q9UHF0 (submitted as IDS reference L), discloses an NKB polypeptide isolated from placenta that is "grossly elevated in pregnancy-induced hypertension and preeclampsia." Applicants note that this polypeptide exactly matches the polypeptide of the present invention. *See* Exhibit A, attached herewith. Thus, it is clear that the NKB polypeptides of the present invention are useful in the diagnosis and treatment of preeclampsia and pregnancy-induced hypertension, as described in the specification.

Applicants point out that post-filing date scientific papers, such as those discussed above, may be used to corroborate Applicants' asserted utility. Legal precedent for the use of post-filing date references in this manner can be found in *In re Brana*, where the Federal Circuit stated that:

> The Kluge declaration, though dated after applicants' filing date, can be used to substantiate any doubts as to the asserted utility since this pertains to the accuracy of a statement already in the specification. *In re Marzocchi*, 439 F.2d at 224 n.4, 169 U.S.P.Q. (BNA) at 370 n.4.
>
> 51 F.3d 1560, 1567, 34 U.S.P.Q.2D (BNA) 1436 (Fed. Cir. 1995).

In response to the Examiner's argument regarding homology, Applicants respectfully assert that the extent to which homology is predictive is moot in the instant case, where Applicants' asserted utility has been proven to be correct. However,

Applicants point out that the NKB polypeptide of the present invention shares a high degree of homology with several mammalian preprotachykinin B polypeptides. Of particular importance is the decapeptide DMHDFFVGLM, which is highly conserved. *See* Exhibit A; *see also* Kotani *et al.*, submitted as IDS reference C. This decapeptide was initially isolated from porcine spinal cord and named "Neuromedin K," and has been identified as the active form of the protein in the porcine and bovine species. *See, e.g.*, Kangawa *et al.*, submitted as IDS reference E. Thus, it is clear that one skilled in the art would appreciate the presence of the conserved decapeptide in the instant polypeptide, and would consider such homology highly predictive of function.

In view of the strong sequence homology to other members of the tachykinin family, the presence of a highly conserved structural domain, and the limited tissue distribution in the placenta, the skilled artisan would have readily appreciated that the asserted utility of detection and/or treatment of reproductive disorders associated with vascularization, such as preeclampsia, was not only more likely than not true, but actually true. Moreover, simply assigning the instant polypeptide to the tachykinin family based on sequence homology, and as human preprotachykinin B in particular based on the conserved decapeptide, would be sufficient to provide a well established use for the diagnosis of pregnancy-related disorders such as preeclampsia. Further, this utility would be readily apparent to one skilled in the art upon reading the instant specification. Applicants note that the courts have routinely determined that evidence of a compound being a member of family of proteins with a well-established utility coupled with evidence demonstrating the activity of the claimed compounds in animals is sufficient corroboration of an asserted utility. *See* M.P.E.P. § 2107.03(II); *In re Jolles*, 628 F.2d 1322, 206 USPQ 885 (CCPA 1980); *see also* Utility Guideline Training Materials, Example 8.

Accordingly, Applicants respectfully submit that the present invention clearly demonstrates a specific, substantial, and credible asserted utility, and a well-established utility that has been fully corroborated by the references discussed above. Thus, Applicants respectfully request that the rejection of claims 24-35 and 56-75 under 35 U.S.C. §101 be reconsidered and withdrawn.

The Examiner has also rejected the claims under 35 U.S.C. § 112, first paragraph, for alleged lack of enablement. In view of the reasons discussed above in response to the rejection under 35 U.S.C. § 101, the claimed invention is supported by a credible, specific,

and substantial utility, as well as a well-established utility. The Examiner "should not impose a 35 U.S.C. § 112, first paragraph, rejection grounded on a 'lack of utility' basis unless a 35 U.S.C. § 101 rejection is proper." M.P.E.P. § 2107(IV). Therefore, since the claimed invention complies with the utility requirements of 35 U.S.C. § 101, Applicants respectfully request that the rejection under 35 U.S.C. § 112, first paragraph, be reconsidered and withdrawn.

CONCLUSION

Applicants respectfully request that the above-made remarks be entered and made of record in the file history of the instant application. Applicants believe that this application is in condition for allowance, and an early notice to that effect is urged. The Examiner is invited to call the undersigned at the phone number provided below if any further action by Applicants would expedite the examination of this application.

If there are any fees due in connection with the filing of this paper, please charge the fees to our Deposit Account No. 08-3425. If a fee is required for an additional extension of time under 37 C.F.R. § 1.136, such an extension is requested and the appropriate fee should also be charged to our Deposit Account.

Dated: August 4, 2003

Respectfully submitted,

By _____

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